Original Article

DOI: 10.7860/JCDR/2013/7479.3589

Normal Values in Healthy Liver in Central India by Acoustic Radiation Force Impulse Imaging

Pathology Section

BABITA RAGHUWANSHI[1], NITI JAIN[2], MANISH JAIN[3]

ABSTRACT

Aim: The aim of this study was to reliably measure and define the normal wave velocity values in a healthy liver by Acoustic radiation force impulse imaging (ARFI) technology in central India.

Subjects and Methods: Fifty two healthy volunteers underwent acoustic radiation force impulse imaging tissue quantification and were enrolled in this prospective study. All patients were examined clinically by a clinician and blood samples were drawn and tested for liver function test and viral markers for hepatitis B virus, hepatitis C virus. The healthy volunteers were then examined by a certified sonologist and twenty-four measurements per subject were obtained and evaluations were performed. Statistical comparison of all mean data was performed with Student's t-test was done. A valueof $p < 0.05$ was considered significant. A comparative analysis was performed, and interclasscorrelation coefficients were calculated.

Results: The sonologist obtained 416 measurements. A statistically significant differencewas found between the mean shear wave velocity values in deep of the right lobe of the liver and the values obtained on the surface of the right lobe (1.2vs1.05 m/s) and between the mean values obtained deep in the right lobe and those obtained deep in the left lobe (1.2vs 1.0 m/s). In almost all cases, the shear wave speeds were between 1 and 2 m/s.

Conclusion: Acoustic radiation force impulse imaging quantification of hepatic tissue is more reproducible when applied to the deeper portion of the right lobe of the liver.

Keywords: Tissue stiffness quantification, Liver Elasticity, Wave velocity values, ARFI

INTRODUCTION

The aim of this study was to reliably measure and define the normal wave velocity values in a healthy liver by Acoustic radiation force impulse imaging (ARFI) technology in central India.

The use of palpation to feel the difference in the mechanical properties of tissues and to differentiate abnormal and normal tissues remains a time-tested diagnostic tool for physicians [1].

Surgeons often detect liver tumours by simple touch at laparotomy that may not have been detected in pre-operative imaging [2].

The use of ARFI as an imaging modality was introduced by Nightingale. ARFI provides multiple parameters and strategies, for example one can map the maximum displacement as points are successively pushed, or the relaxation time following each push [3].

The advantages of ARFI (and the other radiation force based techniques) stem from the fact that anywhere an imaging system can focus; a pushing pulse of radiation force can be 'applied. The disadvantages are that ARFI is a relatively weak effect, thus high intensities and heating of the system and tissue place limits on the resulting displacements [4].

Acoustic radiation force based elasticity imaging methods utilise focused acoustic beams to intra-convert acoustic compressional waves to shear waves through the absorption of acoustic energy, and the tissue response to this acoustic radiation force is monitored to derive information about the underlying tissue structure and stiffness. Elasticity imaging methods involving acoustic radiation force have been under investigation for several years [5-11]. These methods offer some advantages over those requiring external excitation: the force is applied directly to the region of interest, thus smaller stresses are used, and challenges associated with coupling the excitation to the desired tissue region are diminished.

For the generation of images portraying relative differences in tissue stiffness, ARFI imaging has been developed, in which the tissue displacement response is monitored within the ROE, and image data are generated by sequentially interrogating different lateral positions, as is done in conventional 2D ultrasound imaging [12].

Imaging techniques

Acoustic radiation force impulse imaging (AcusonS2000 ultrasound system, Siemens Healthcare) was performed with convex probes (4C1, Siemens Healthcare), tissue harmonic imaging (4MHz), and a mechanical index of 1.7. To quantify the wave propagation speed, the quantitative implementationof acoustic radiation force impulse technology (Virtual Touch tissue quantification, Siemens Healthcare) was used. All healthy volunteers underwent imaging in the supine position. The anatomic location used for scanning did not include blood vessels or biliary structures. An acoustic push pulse was transmitted, and localised displacements were generated into the target region. The response was monitored with ultrasound. Quantification of shear wave velocity (measured in meters/ second) was performed, and a numeric value proportional to the tissue stiffness based on multiple measurements automatically made for the location was reported.

Virtual Touch Tissue Imaging and Virtual Touch tissue quantification are the first implementation of ARFI and are promising in identifying early stages of liver diseases causing cirrhosis. Early studies show that Virtual Touch Tissue Quantification proved sensitive in diagnosing fibrosis and distinguishing it from normal liver and cirrhosis.

"Virtual Touch Tissue Quantification is a promising procedure for quantifying the liver fibrosis stage using B mode controlled ultrasound in patients with viral hepatitis."

Acoustic radiation force is a phenomenon associated with the propagation of acoustic waves in attenuating media. Attenuation includes both scattering and absorption of the acoustic wave. Attenuation is a frequency dependent phenomenon, and in soft tissues it is dominated by absorption. The speed at which shear waves propagate in tissue can be used to quantify the shear modulus of the tissue. Acoustic radiation force-based imaging modalities are being studied to non-invasively characterise the liver without the need for liver biopsy.

Acoustic Radiation Force Impulse Imaging is a New Technique to Assess Liver Elasticity.

Study Sample

Our study included 52 subjects without known hepatic pathology ("normal" subjects), voluntary blood bank donors who agreed to participate in our study.

None of the healthy volunteers had a history of liver disease (acute or chronic). We performed additional tests in this subgroup (such as liver function tests, viral markers, abdominal ultrasound, etc.). Also, none of them had a severe disease such as congestive heart failure, renal failure, or diabetes.

Fifty Two healthy volunteers (eight women, 44 men; mean age, 37.52 years; range, 14–61 years) underwent acoustic radiation force impulse imagingtissue quantification and were enrolled in thisprospective study. All subjects signed a written in formed consent form before the examination. Because our intention was to study healthy liver,only persons with normal liver function tests and with hepatitis B virus surface antigen & hepatitis C virus negative status were enrolled. The inclusion criteria were certain absence of a history of focalor diffuse hepatic disease (assessed with clinical examination, laboratory data, and conventional ultrasound) and the good visualisation of the liver with conventional ultrasound. All Subjects were also clinically examined for fitness. No subject reported use of medications or illegal drugs or alcohol at the time of the imaging examination.

All volunteers were examined by a radiologist, who had experience and training in acoustic radiation force impulse technique. The measurements were made on patients lying in dorsal decubitus with the right arm in maximal abduction.

For the right hepatic lobe, two subcostal scans were obtained during a breath-hold after subtle inspiration, and two intercostal scans were obtained during a breath-hold without preparatory inspiration.

For the left hepatic lobe, two subcostal scans were obtained during a breath-hold after subtle inspiration, and two intercostal costal scans were obtained during a breath-hold without preparatory inspiration.

Subtle inspiration was defined asa simple inspiration sufficient for performance ofthe subcostal measurements. For both the right and the left hepatic lobes, measurements were obtained on the surface and deep. For surface measurements, the area scanned (AS) was as superficial as possible, immediately under the surface of the liver. For deep measurements, the AS was located at the maximum depth evaluable with the system (5.5 cm) in the right hepatic lobe and as deep as possible inthe left hepatic lobe. During each evaluation, the sonologist was careful not to include vessels and biliarystructures in the AS.

Total of eight measurement were performed per subject. With acoustic radiation force impulsetissue quantification, shear wave speed in solid materials is expressed as a numerical value. Thus measurements expressed by the system as having no numerical value, as not available, or as XXXX or 0, were not taken into consideration and not included in reaching the defined number of measurements. From all measurements performed by the sonologist, mean wave velocity values for the left and the right hepatic lobes and for the entire liver were obtained.

STATISTICAL ANALYSIS

All measurements independently obtained were analysed for the differences between the mean values derived as follows: (a) during a breath-hold after subtle inspiration and without inspiration for both hepatic lobes, (b) The subcostal and intercostal area of both the lobes of liver were scanned and wave velocity values were obtained for deep in and on the surface of the left hepatic lobe and the right hepatic lobe.

Statistical comparison on all mean wave values was performed with Student's t-test, and $p<0.05$ was considered statistically significant.

We calculated the mean value of Liver stiffness (LS) for the whole group, as well as for different age groups. For a statistical study of quantitative variables, the mean and standard variations were calculated. One-way ANOVA test and t-tests were performed to compare mean values of LS in various age subgroups and in men vs. women [Table/Fig-1].

RESULTS

A total of 416 measurements were performed. As per [Table/Fig-2]; no statistically significant difference was observed between the mean wave velocity values obtained deep in and on the surface (both subcostal and intercostal) of right hepatic lobe. This may be due to the fact that right hepatic lobe hasthickerparenchyma andpossibly it is far from the perihilar area and therefore the effect of vascular pulsation is minimized.

A statistically significant difference ($p < 0.05$) was observed between the mean wave velocity values obtained in deep intercostal and on the surface intercostal area of the right hepatic lobe (1.24 vs. 1.05 m/s) and in both subcostal and intercostal area of left hepatic lobe.

The total mean wave velocity values derived from all measurements performed in each subject are summarized in [Table/Fig-3 and 4]. In almost all cases, shear wave velocity was between 1 and 2 m/s, as all subjects enrolled in this study had common characteristics. A statistically significant difference ($p < 0.05$) was found in all comparisons (deep, surface, total mean value) performed on the left hepatic lobe. No statistically significant difference ($p > 0.05$) was found in any of the comparisons (deep, surface, total mean value) performed on the right hepatic lobe except the right deep intercostal wherein the statistically significant difference ($p<0.05$) was found.

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Men	46	85.2	85.2	85.2
	Women	8	14.8	14.8	100.0
	Total	54	100.0	100.0	

[Table/Fig-1]: Comparison of mean value of LS in men vs. women

	N	Minimum	Maximum	Mean	Std. Deviation
SCSURFACER	52	.62	2.82	1.2906	.40401
SCDEEPR	52	.50	2.71	1.2373	.45656
RSURFACEic	52	1	2	1.24	.180
RDEEPSURIC	52	.62	1.47	1.0565	.24909
LSURFSC	52	1	5	1.58	.671
LDEEPSC	52	.60	3.06	1.0487	.42615
LSURFIC	52	.71	3.70	1.4629	.51622
LDEEPIC	52	.51	2.76	1.0012	.41896
Valid N (listwise)	52				

[Table/Fig-2]: Descriptive Statistics

	N	Minimum	Maximum	Mean	Std. Deviation
HB	52	9.6	14.3	13.062	1.1049
TLC	52	5200	11500	7640.38	1686.307
PLT	52	1.50	3.80	2.1954	.57119
AGESEX	52	14	61	37.52	9.731
TBILI	52	.5	5.8	.830	.7860
DBILI	52	.1	2.6	.352	.3534
SGPT	52	15	64	34.69	9.777
SGOT	52	18	67	36.40	9.034
PRT	52	5.8	7.8	6.894	.4399
ALKPO4	51	51	209	88.92	22.516
Valid N (listwise)	51				

[Table/Fig-3]: Descriptive Statistics

	SEX	N	Mean	Std. Deviation	Std. Error Mean
SCSURFACER.	Men	46	1.2941	.35253	.05198
	Women	8	1.3325	.64791	.22907
SCDEEPR	Men	46	1.2552	.58163	.08576
	Women	8	1.5100	.71488	.25275
R.SURFACE IC	Men	46	1.27	.279	.041
	Women	7	1.29	.208	.079
RDEEPSURIC	Men	46	1.0767	.26597	.03922
	Women	8	1.0075	.16016	.05662
LSURFSC	Men	45	1.60	.700	.104
	Women	8	1.65	.494	.175
LDEEPSC	Men	46	1.0159	.33417	.04927
	Women	8	1.2000	.78577	.27781
LSURFIC	Men	46	1.4496	.56838	.08380
	Women	8	1.9025	.86854	.30708
LDEEPIC	Men	46	.9187	.32439	.04783
	Women	8	1.4213	.61033	.21578

[Table/Fig-4]: Descriptive Statistics

SC surface = Subcostal on surface, R = Right, SC Deep = Subcostal Deep, Surface IC = Intercostal on surface, Deep IC = Deep intercostal, L = Left

DISCUSSION

Currently, in clinical practice, there are three available methods for the evaluation of liver fibrosis: liver biopsy which is still considered to be the gold standard, serological markers of fibrosis, and more recently ARFI a new simple non-invasive method used to measure liver stiffness.Recently the non-invasive methods have become more and more popular. The aim of this study was to reliably measure and define the normal wave velocity values in a healthy liver by Acoustic radiation force impulse imaging (ARFI) technology.

Liver fibrosis is a very important factor associated with prognosis in chronic hepatitis (viral and non-viral). Hence, a precise evaluation of the severity of fibrosis is needed in order to perform a correct staging and to take decisions regarding the treatment

Currently, the biopsy examination of the liver is considered to be the "gold standard" method for evaluating fibrosis [1]. However, the liver biopsy (LB) is not a perfect method due to: intra- and interobserver variability [13,14] sampling variability [15] and, last, the fact that LB is an invasive method, with morbidity and mortality greater than 0.

Considering all these facts, non-invasive methods for the evaluation of liver fibrosis have been developed in the last few years, in order to replace LB, among them liver stiffness (LS) evaluation by means of ARFI using a Siemens 2000 is one of the important methods relied upon by gastroenterologist.

Methods designed to image the mechanical properties of tissues with improved sensitivity and specificity over clinical palpation have been under investigation for many years [16].

ARFI is a type of strain EUS whereby tissue is excited internally by a focused ultrasound pulse, instead of external (manual or physiological) compression [17-20]. As the ultrasound pulse travels through the tissue, soft tissue experiences larger displacement than hard tissue. After the excitation and displacement by the pulse, the tissue relaxes to its original configuration. The tissue displacement by the original push pulse can be measured using the application of several short-time pulse echoes, which provides data for comparison with the reference image [17,18-20]. The technique also results in a qualitative colour-coded or greyscale elastogram depicting relative tissue stiffness. This method has the advantage of imaging deeper tissue, not accessible by superficial external compression, and has been used mainly for liver, thyroid and breast imaging [17-20].

There are several points to be considered before standardizing the normal values of liver in healthy individuals. The intra observer variability, the difference in thickness of liver parenchyma in the right and left hepatic lobes and the effect of vascular pulsation due to proximity of left hepatic lobe from perihilar area. The limitation of our study despite several advantages was the inability to correlate the normal LS values in central Indian population with histologically proven normal liver, as this is not ethically permitted.

There have been several studies on intra observer variability of ARFI by different users and majority of studies have found excellent correlation in values by different sonologists [21].

The difference in the ARFI values of right lobe and left lobe of liver may be due to the difference in thickness of parenchyma between the two lobes.

The difference in ARFI values in right hepatic lobe deep subcostal region and left hepatic lobe deep subcostal area may be due to proximity of left hepatic lobe to perihilar region.

Last, but not least, the normal range of LS measurements must be established, in order to differentiate the normal liver from the fibrotic liver.

In the above study the normal range of liver stiffness in Indian population was in the range of 1.0-1.29 m/s except in the left hepatic lobe intercostal region. This may be due to the proximity of left hepatic lobe to perihilar region and also due to difference in the thickness of hepatic parenchyma between the right and left hepatic lobes.

REFERENCES

[1] Yogesh K Mariappan, Kevin J Glaser, and Richard L Ehman*. Magnetic ResonanceElastography: A Review. *Clin Anat.* 2010 July ; 23(5): 497–511.

[2] Elias D, Sideris L, Pocard M, de Baere T, Dromain C, Lassau N, et al. Incidence of Unsuspected and Treatable Metastatic Disease Associated With Operable Colorectal Liver Metastatis Discovered Only at Laparotomy (and Not Treated When Performing Percutaneous RadiofrequencyAblation). *Ann SurgOncol.* 2005; 12:298–302. [PubMed: 15827682]

[3] Nightingale K R, Palmeri M L, Nightingale R W and Trahey .G E 2001 On the feasibility of remote palpation using acoustic radiation force. *J. Acoust. Soc. Am.* 110625–34.

[4] Palmeri M L and Nightingale K R 2004 On the thermal effects associated with acoustic radiation force impulse imaging IEEE Trans. Ultrason. *Ferro electr. Freq. Control.* 51551–65.

[5] Sarvazyan A, Rudenko O, Swanson S, Fowlkes J, Emelianov S. Shear Wave Elasticity Imaging: A New Ultrasonic Technology of Medical Diagnostics. *Ultrasound Med Biol.* 1998; 24(9):1419–1435.[PubMed: 10385964]

[6] Fatemi M, Greenleaf J. Ultrasound-Stimulated Vibro-Acoustic Spectrography. *Science.* 1998;280:82–85. [PubMed: 9525861]

[7] Nightingale KR, Soo MS, Nightingale RW, Trahey GE. Acoustic Radiation Force Impulse Imaging:In vivo Demonstration of Clinical Feasibility. *Ultrasound Med Biol.* 2002; 28(2):227–35. [PubMed: 11937286]

[8] Bercoff J, Tanter M, Fink M. Supersonic shear imaging: a new technique for soft tissue elasticitymapping. *IEEE Trans Ultrason, Ferroelec, Freq Contr.* 2004; 51(4):396–409.

[9] Viola F, Walker WF. Radiation force imaging of viscoelastic properties with reducedartifacts. *IEEE Trans Ultrason Ferroelectr Freq Control.* 2003 Jun; 50(6):736–42. [PubMed: 12839188]

[10] Lizzi FL, Muratore R, Deng C, Ketterling J, Alam K, Mikaelian S, et al. Radiation-Force Techniqueto Monitor Lesions During Ultrasonic Therapy. *Ultrasound Med Biol.* 2003; 29(11):1593–1605. [PubMed: 14654155]
[11] Konofagou E, Thierman J, Hynynen K. A focused ultrasound method for simultaneous diagnosticand therapeutic applications–a simulation study. *Phys Med Biol.* 2001 Nov; 46(11):2967–84.[PubMed: 11720358]
[12] Nightingale K, Bentley R, Trahey GE. Observations of Tissue Response to Acoustic Radiation Force: Opportunities for Imaging. *Ultrasonic Imaging.* 2002; 24:100–08. [PubMed: 12199416]
[13] Regev A, Berho M, Jeffers LJ, et al. Sampling error and intraobserver variation in liver biopsy in patients with chronic HCV infection. *Am J Gastroenterol* 2002; 97: 2614-18.
[14] Persico M, Palmentieri B, Vecchione R, Torella R, de SI. Diagnosis of chronic liver disease: reproducibility and validation of liver biopsy. *Am J Gastroenterol.* 2002; 97: 491-492.
[15] Ratziu V, Charlotte F, Heurtier A, et al. Sampling variability of liver biopsy in nonalcoholic fatty liver disease. *Gastroenterology.* 2005; 128: 1898-1906.
[16] Kathy Nightingale .Acoustic Radiation Force Impulse (ARFI) Imaging: a Review. *Curr Med Imaging Rev.* 2011 November 1; 7(4): 328–339.
[17] Li Y, Snedeker JG. Elastography: modality-specific approaches, clinical applications, and research horizons. *Skeletal Radiol.* 2011;40:389–97.
[18] Goertz RS, Zopf Y, Jugl V, Heide R, Janson C, Strobel D, etal. Measurement of liver elasticity with acoustic radiation force impulse (ARFI) technology: an alternative noninvasive method for staging liver fibrosis in viral hepatitis. *Ultraschall Med.* 2010;31:151–55.
[19] Tozaki M, Isobe S, Fukuma E. Preliminary study of ultrasonographic tissue quantification of the breast using the acoustic radiation force impulse (ARFI) technology. *Eur J Radiol.* 2011;80:e182–87.
[20] Friedrich-Rust M, Romenski O, Meyer G, Dauth N, HolzerK, Gru¨nwald F, et al. Acoustic Radiation Force Impulse Imaging for the evaluation of the thyroid gland: a limited patient feasibility study. *Ultrasonics.* 2012;52:69–74.)
[21] MirkoD'Onofriol, Anna Gallott I, Roberto PozziMucelli, D'Onofrio M, Gallotti A, Poz. Tissue Quantification With Acoustic Radiation Force Impulse Imaging: Measurement Repeatability and Normal Values in the Healthy Liver: *AJR* 2010;195:132–36.

PARTICULARS OF CONTRIBUTORS:
1. Assistant Professor, Department of Transfusion Medicine, L.N. Medical College & Research Centre, India.
2. Assistant Professor, Department of Radio Diagnosis, L.N. Medical College & Research Centre, India.
3. Assistant Professor, Department of Medicine, L.N. Medical College & Research Centre, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Babita Raghuwanshi,
Department of Transfusion Medicine & Blood Bank,
All India Institute of Medical Sciences, Sijua, Patrapada, Bhubaneswar-751019, Odisha, India.
Phone: 9492776417, E-mail: drjyothimds@gmail.com

FINANCIAL OR OTHER COMPETING INTERESTS: None.

Date of Submission: **Aug 26, 2013**
Date of Peer Review: **Oct 08, 2013**
Date of Acceptance: **Oct 22, 2013**
Date of Publishing: **Nov 10, 2013**